Testimony
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Pandemic Influenza Preparedness

Statement of
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Mr. Chairman and members of the Committee, I am Dr. Bruce Gellin, Director of the National Vaccine Program Office at the Department of Health and Human Services and the Chair of the Secretary's Influenza Preparedness Task Force. I am pleased to appear before you today to discuss avian influenza and the measures the Department is taking to prepare for an influenza pandemic.

An influenza pandemic is a global outbreak of disease that occurs when a new influenza A virus emerges in the human population, causes serious illness, and then spreads easily from person to person worldwide. Three influenza pandemics have occurred during the 20th century. The most deadly influenza pandemic outbreak was the 1918 Spanish flu pandemic, which caused illness in roughly 20 to 40 percent of the world's population and resulted in at least 500,000 deaths in the United States and 20-40 million deaths worldwide.

Many public health experts believe the threat of a pandemic is now greater than it has been in decades. A report issued by the World Health Organization warns that the virus may be evolving in ways that increasingly favor the start of a pandemic. In addition, the ecology of the disease and behavior of the virus have changed and are creating multiple opportunities for a pandemic virus to emerge. This is in large part because of the influenza H5N1 virus, the so-called "bird flu" that is established and endemic in many different species of birds in Asia. As these avian viruses continue to evolve and spread in animals, the possibility increases that an avian virus will recombine with a human virus to cause a novel and easily transmitted influenza virus strain in humans. Based on data that has

been made available to the World Health Organization on the impact of the H5N1 virus in Asia, more than half of the people who are known to have been infected with this virus have died from this infection. This is not an exact estimate of the mortality rate for this disease because only people who have become sick enough to go to the hospital have actually been diagnosed with the infection. There may be many more people who were infected without being diagnosed.

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While scientists in 1918 had very little idea of what was happening until it was too late, we have time - and still have time - to prepare for the next global pandemic, and we should consider ourselves warned. As Secretary Leavitt stated at the World Health Assembly in May, "We are working on pandemic preparedness on borrowed time. When this event occurs, our response has got to be immediate, comprehensive and effective."

The Department has made preparedness for an influenza pandemic one of its highest priorities and it is a critical component of Secretary Leavitt's 500-day plan. In May, at the World Health Assembly -- the annual meeting of Ministers of Health from around the world -- the Secretary spoke of the Department's commitment in this area. He encouraged global transparency, strengthened surveillance and communications, and timely sharing of information and clinical specimens as a critical component of our global preparedness. Secretary Leavitt also urged international collaborations among developed and developing countries to control the virus among humans and animals. Further, the World

Health Assembly passed a resolution on pandemic preparedness that was originally offered by the U.S. as a blueprint for global action.

We have expanded and enhanced the planning and preparedness activities that are critical to improving the effectiveness of a national and worldwide response that would decrease the impact of a pandemic should it occur. HHS has increased support for pandemic influenza activities and is engaged in several efforts to enhance the nation's preparedness for such an outbreak. HHS supports pandemic influenza activities in several key areas including: public health preparedness, research, vaccine development and production, antiviral stockpiling, and surveillance.

In addition, on the national front, the Department has been actively revising the draft Pandemic Influenza Preparedness and Response Plan that was issued last year 2004. This Plan describes a coordinated strategy to prepare for and respond to an influenza pandemic. The 2005 update of the plan will address many of the outstanding policy issues and provide the guidance to state and local health departments, the healthcare system, the public and the international community. HHS will regularly be revising and reworking the plan in order to provide current thinking and current science.

Earlier this month, Secretary Leavitt established a Department-wide Influenza Task Force to coordinate all HHS activities affecting the public health

preparedness for seasonal influenza outbreaks and an influenza pandemic. The Task Force's near term objective is to ensure completion of an updated pandemic plan. Long term objectives include an effective and efficient global surveillance network for outbreaks of influenza-like illness in humans and animals, and interoperable local, state, and federal government response plans for influenza outbreaks within the United States – including strategies and plans for effective coordination with response partners, public and private, and timely communication with the public.

To address the outstanding policy issues that will be incorporated into the Department's 2005 update of the Pandemic Preparedness and Response Plan, a joint working group of the National Vaccine Advisory Committee (NVAC) and Advisory Committee on Immunization Practices (ACIP) has been established to provide guidance to the Department. In addition to representatives from each of these federal advisory committees, working groups have had representation from public health and health care organizations, industry, federal agencies and other Departments. Next month, a joint meeting of NVAC and ACIP will review the findings of the working group and develop recommendations for prioritizing the use of pandemic vaccine and antiviral drugs.

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In addition to the guidance embodied in the Department's Pandemic Influenza Preparedness and Response Plan, HHS is taking many proactive steps to prepare and plan for a pandemic. One of these critical elements is the inclusion

of antiviral drugs in the Strategic National Stockpile (SNS). Another component of our preparedness is ensuring sufficient domestic surge capacity for influenza vaccine production.

Influenza antiviral medications have long been used to limit the spread and impact of institutional influenza outbreaks. These drugs may serve an important role in stemming a developing pandemic and in treating patients early in their influenza infection, with greatest effect if the drug is administered within 48 hours of onset of symptoms. We plan to utilize antiviral drugs as one influenza countermeasure to help mitigate influenza impact. Laboratory analyses demonstrate that these drugs appear to have activity against the H5N1 influenza strains in Asia; however, we have limited data to date about their effectiveness in treating patients infected with this virus. To date, there are some anecdotal reports of human H5N1 infections that have advanced despite early treatment, but anecdotes are not data. We need better data from the field to guide our decisions.

It is worrisome that M2 inhibitors, one of only two classes of antiviral drugs for influenza is not likely to be useful in fighting the H5N1 virus. As reported recently in the Washington Post, it appears that the use of the antiviral drug amantadine (an M2 inhibitor) in livestock feed in Asia is responsible for the emergence of resistance to the virus. This underscores the critical importance that these drugs

be used appropriately so as not to induce further resistance by the virus and removing this drug from our armamentarium.

The bottom line is that today, neuraminidase inhibitor drugs are the only class of antivirals available that can take on this virus. The United States has ordered and received delivery of approximately 2.3 million treatment courses of the antiviral, oseltamivir (Tamiflu®), a neuraminidase inhibitor, for the SNS and is currently in active discussions with Roche, the maker of this drug, to increase our national reserve. In addition, we are exploring the potential to include the other antiviral drug in this class, zanamivir (Relenza®), in the SNS. The Department also appreciates Congress' inclusion of $58 million in the FY 2005 Emergency Supplemental Appropriations Act for Defense, the Global War on Terror, and Tsunami Relief to procure additional influenza countermeasures for our Strategic National Stockpile.

In addition to antiviral drugs for the treatment or prevention of influenza, vaccination is one of the most important tools we have for pandemic preparedness, as it is the primary means to prevent morbidity and mortality during an epidemic. Because a pandemic is by definition the introduction and spread of a novel strain, there are major implications for vaccine development.

- First, the majority of the population is likely to be susceptible. NIH's clinical studies on the H5N1 vaccine will be available in the coming weeks and will provide critical information about the immune response and safety

profile of this candidate vaccine. Because humans' immune systems have not encountered this novel virus before, we expect that two doses of a vaccine might be needed for effective immunity, but we will let the science speak for itself when the results of these clinical trails are available.

- In addition we need to ensure that we have adequate capacity to produce a vaccine once its proof of principle has been established. To this end, we recognize that modern transportation and trade are likely to rapidly accelerate the global spread of influenza. Given our experience with the infectiousness of influenza, we assume that an outbreak somewhere is very likely to become a health threat anywhere…and potentially everywhere. As a consequence, our planning assumption is that in the setting of a pandemic emergency, there will be worldwide demand for vaccine and therefore vaccine produced outside of the United States will not be available for domestic use.

From a preparedness perspective, it is important to acknowledge that that the perfect vaccine cannot be prepared far in advance and stockpiled, since the vaccine has to be tailored to match the circulating virus. In addition to the vaccine that has been developed for NIH's clinical vaccine trials, we have asked Sanofi Pasteur develop 2 million doses of H5N1 vaccine based on the virus that was in circulation in Asia last year. We don't yet know whether the H5N1 vaccine will provide protection against a pandemic strain that might emerge, but this action provides us with some vaccine that has potential use, while also providing

at least one manufacturer with significant experience working with this strain in commercial-scale manufacturing facilities and is likely to translate into time saved in the development of a pandemic vaccine should the need arise. It is possible that the pandemic virus will continue to evolve (drift), such that this vaccine could be a poor match for and have limited effectiveness against the circulating strain but we chose to take advantage of the narrow window of opportunity in the manufacturing cycle so that this vaccine could be made without interfering with the production of the annual influenza vaccine that is made in the same facility.

Developing and producing a pandemic vaccine is further compounded by a fragile vaccine supply system. This fragility was documented during the past influenza season, when one of the two large influenza vaccine manufacturers could not supply vaccine to the U.S. market. While we are optimistic that there are new influenza manufacturers coming to US market, these ongoing problems with annual influenza production highlight the need for greater diversification of the U.S. domestic production capacity and the parallel need to improve demand for a life-saving vaccine that remains underutilized.

All U.S. licensed influenza vaccines are developed from viruses that are grown in embryonated eggs in a process unique for influenza vaccine. Influenza vaccine manufacturing happens when a strain of the virus adapted to grow in eggs is injected separately into millions of fertilized eggs, which are subsequently incubated to allow the influenza virus to grow. These egg-grown viruses are

inactivated, purified, tested for potency, blended into the trivalent vaccine, and filled into syringes or vials. The number of influenza vaccine doses produced is limited by the capacity of the production facilities, the availability of embryonated eggs, the yield of influenza virus from each egg, and the length of time that manufacturing takes.

HHS has developed several influenza vaccine supply initiatives to address annual as well as pandemic influenza vaccine. The objectives of these initiatives are to

- secure and expand U.S. influenza vaccine supply
- diversify production methods, and
- establish emergency surge capacity.

To support these activities, HHS received $50 million in FY2004 and $99 million in FY2005. The President's Budget for FY2006 includes an additional $120 million to further strengthen this component of the overall pandemic influenza preparedness efforts.

Because influenza vaccine is produced to meet the seasonal demand in the fall, production also is seasonal and embryonated eggs have not been available to manufacturers year-round. Moreover, although some excess supply may be available to support additional influenza vaccine production or provide security if the flocks that produce eggs for vaccine production are affected by avian influenza or other illness, this excess is limited creating vulnerability to supply

disruption. To enhance influenza vaccine supply security, HHS issued a five-year contract to Sanofi-Pasteur of Swiftwater, Pennsylvania, on September 30, 2004 for $40.1 million. Under this contract, Sanofi-Pasteur has begun to change its flock management strategy to provide a secure, year-round supply of eggs suitable for influenza vaccine production at full manufacturing capacity. It also will increase the number of egg-laying flocks by 20% to provide contingency flocks in case of an emergency. These eggs may be used to support additional production of annual influenza vaccine in the event of a vaccine shortage with the doses being delivered later in the fall. Additionally, this contract provides for production of annual investigational lots of prototype pandemic influenza vaccines. For example, this summer, Sanofi-Pasteur will manufacture an H7N7 virus vaccine that will be evaluated through the National Institutes of Health Vaccine Treatment and Evaluation Units.

Diversification of influenza vaccine production methods also will help strengthen the system. Cell culture technology is a well-established vaccine production method for other vaccines such as the inactivated poliovirus vaccine, and two companies have registered their cell-culture based influenza vaccine technology in Europe. This production technology does not require eggs as a substrate for growth of vaccine virus, thereby avoiding the vulnerabilities associated with an egg-based production system. It also may be more amenable to surge capacity production when influenza vaccine production will be needed to be expanded rapidly, such as at the time of a pandemic. Finally, the new cell-based influenza

vaccines will provide an option for people who are allergic to eggs and therefore unable to receive the currently licensed vaccines.

Earlier this spring, Secretary Leavitt announced that the Department of Health and Human Services issued a five-year contract on March 31, 2005 to Sanofi-Pasteur for $97.1 million to develop cell culture influenza vaccine technology and conduct clinical trials, with the goal of obtaining an FDA license for this vaccine. Under this advanced development contract, the company has also committed to manufacturing this vaccine at a U.S.-based facility with a capacity to manufacture 300 million doses of monovalent (single strain) pandemic vaccine over a one-year period. However, given timelines for vaccine development and clinical trials, and for construction and validation of manufacturing facilities, additional influenza vaccine supply from this source is unlikely to be available for at least five years.

These important steps to strengthen our national influenza vaccine supply through assuring the egg-supply and diversifying and expanding production capacity will be followed this year by additional measures to increase influenza vaccine production capacity and expand the number of influenza vaccine doses made using that capacity. Supported by the pandemic influenza vaccine initiative in the FY'06 budget request for $120 million, we posted synopses of three additional areas where we believe strategic investments move us toward achieving annual and pandemic influenza vaccine supply goals in the March 17, 2005 edition of FedBizOpps. On April 29, 2005, the first of these requests for

proposals was posted, providing support for the development of cell-culture based and recombinant pandemic influenza vaccines. This contract, leading to the licensure and U.S. production of a next-generation influenza vaccine, will further increase production capacity and diversification of the manufacturing base.

Whereas building new influenza vaccine production facilities is one approach to expand the influenza vaccine supply, other strategies also can increase the number of influenza vaccine doses produced. Influenza vaccine is manufactured in a series of steps – developing an influenza virus master seed for vaccine production, inoculating the virus into eggs, growing, harvesting, purifying, splitting, formulating, and filling it into vials or syringes. Improving efficiency at any step in this process can increase the eventual yield and number of vaccine doses produced. Thus, a second area of emphasis will be to support improvements of the manufacturing process to increase overall influenza vaccine production at current manufacturing facilities.

The third area of emphasis will provide support for research and development, leading to licensure of strategies that will stretch the number of vaccine doses produced by decreasing the amount of influenza virus antigen that is needed in each dose. The concept underlying these “dose-stretching” strategies is that by changing either the influenza vaccine or the way it is administered, one can improve the immune response to vaccination and provide protection while using

less of the vaccine antigen. By using less antigen in each vaccine dose, the number of doses that can be made at any level of production capacity would be multiplied. The two most promising antigen-sparing approaches are either to add an adjuvant (a substance that stimulates the immune response to a vaccine formulation), or administering the vaccine into the skin (similar to the approach used in a skin test for tuberculosis) where large numbers of potent immune cells are located. Both strategies have been evaluated in several clinical trials and have the potential to expand influenza vaccine supply several-fold if they prove effective in further clinical trials and are approved for licensure.

The increase in the FY 2006 President's Budget request will support ongoing activities to ensure that the Nation will have an adequate influenza vaccine supply to respond better to yearly epidemics and to influenza pandemics. While issuing the requests for proposals and completing the contracts is only the first step toward the development of an expanded, diversified, and strengthened influenza vaccine supply, the U.S. is leading the global effort to develop vaccines and vaccine technologies to meet this challenge.

Stemming the spread of the epidemic will require close coordination between the agriculture and health sectors and among affected countries, donor nations and international organizations dedicated to promoting the health of humans, livestock and wildlife. The FY 2005 Emergency Supplemental Appropriations Act for Defense, the Global War on Terror, and Tsunami Relief included $25 million

to prevent and control avian influenza in Southeast Asia. Detailed joint planning is already underway with the Department of State (with HHS focusing on human health) and USAID working (with USDA focusing on projects on animal health and related issues). In this way, the two agencies' plans will be complementary, not duplicative.

With this funding, we will support activities with the following goals:

- Strengthening the capacity of affected countries to conduct disease surveillance, prevention, and response, primarily in the most affected countries –Vietnam, Cambodia, and Laos
- Limiting the spread of the H5N1 avian influenza virus among birds.
- Limiting the spread of the H5N1 avian influenza virus from animals to humans.
- Reducing the potential economic consequences of avian influenza for affected countries.

The threat of a pandemic is real, whether it comes in 10 days or 10 years from now and whether it is H5N1 or another emerging strain. In anticipation of the next pandemic, we are working along with the global health community on this public health threat. The US has taken a leadership role in this area. We recognize the challenge before us, and know that we must all continue to be diligent and prepare for a potential public health threat of unimaginable magnitude.

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Thank you for your attention to my remarks this morning – and more importantly to the attention that you have paid to pandemic influenza. I would be happy to answer any questions from the Committee.